Scientific Abstract

The inherited blood coagulation disorder hemophilia A results from deficiency in the expression or function of FVIII. Treatment of moderate and severe hemophilia A involves intravenous infusion of plasma-derived or recombinant FVIII concentrates. A major limitation of current therapy is the short half-life of infused FVIII.

The MiniAdFVIII vector is a minimal (gutless) adenovirus vector designed to restore production of human FVIII by delivering the entire FVIII complementary deoxyribonucleic acid to somatic cells. Pre-clinical data indicates that the vector will not express adenoviral antigens *in vivo*, thus minimizing potential immune responses and resulting in long-term persistence of the vector and expression of the transgene. Nonclinical pharmacology studies have indicated that physiological levels of hFVIII were produced *in vivo*, and these levels persisted for an extended period of time (approximately 1 year), resulting in phenotypic correction in hemophilic mice. Importantly, pre-clinical studies performed at several independent laboratories (including our own) have indicated that gutless adenoviral vectors have improved safety and efficacy profiles compared to earlier generation adenoviral vectors currently in clinical trails.

The objective of this Phase 1 study is to evaluate through dose escalation in defined increments the safety of intravenous infusion of MiniAdFVIII vector in severe hemophilia A patients without inhibitors. Additional objectives of this study are as follows: (1) to evaluate through dose escalation in defined increments the ability of an intravenous infusion of MiniAdFVIII vector to produce circulating, functional levels of FVIII, (2) to evaluate the effect of MiniAdFVIII vector therapy on the frequency and severity of bleeding events following defined dose escalation, (3) to evaluate immunologic responses following the administration of MiniAdFVIII vector by monitoring anti-adenoviral and anti-FVIII antibody titers in blood, and (4) to determine the functional FVIII expression profile by measuring the level, time course, and duration of functional and circulating FVIII.

The proposed study consists of a 7-day Screening Phase, a 1-day Treatment-Phase, a 12-week Post-treatment Phase and a 2-year Follow-up Phase. During the Screening Phase, the general clinical status of the patient will be determined. In addition, FVIII levels and FVIII inhibitor levels will be assessed. Two dose levels will be evaluated in this study (6 patients enrolled into two cohorts). In the Treatment Phase, MiniAdFVIII (1.4×10^{10} vp/kg or 4.3×10^{10} vp/kg) will be administered by intravenous infusion. The study will begin with the first cohort of three patients receiving a single dose of MiniAdFVIII. Dosing of each of the three patients in each cohort will be separated by at least two weeks. After 28 days of observations of each study subject at the first dose level to evaluate safety and immunologic responses, the second cohort of three patients will be administered the higher dose level. During the Post-treatment Phase of the study, patients will be closely monitored for adverse events. Weekly monitoring until Week 12 will include physical examinations, vital signs, liver function assessment, as well as clinical chemistry, and hematology, and urinalysis assessments. Serum FVIII levels and the development of FVIII inhibitors will be assessed. MiniAdFVIII levels will be monitored in the blood and urine. Anti-adenoviral serotype 5 antibodies will also be monitored in the blood. Follow-up Phase monitoring will be performed monthly for approximately 2 years or until no ongoing safety concerns exist; liver function, clinical chemistry, and hematology, and urinalysis will be assessed monthly.